

Incremental Prognostic Use of Left Ventricular Global Longitudinal Strain in Asymptomatic/Minimally Symptomatic Patients With Severe Bioprosthetic Aortic Stenosis Undergoing Redo Aortic Valve Replacement

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Background—With improved survival of patients undergoing primary bioprosthetic aortic valve replacement (AVR), reoperation to relieve severe prosthetic aortic stenosis (PAS) is increasing. Timing of redo surgery in asymptomatic/minimally symptomatic patients remains controversial. Left ventricular (LV) global longitudinal strain (GLS) is a marker of subclinical LV dysfunction. In asymptomatic/minimally symptomatic patients with severe PAS undergoing redo AVR, we sought to determine whether LV-GLS provides incremental prognostic use.

Methods and Results—We studied 191 patients with severe bioprosthetic PAS (63±16 years, 58% men) who underwent redo AVR between 2000 and 2012 (excluding mechanical PAS, severe other valve disease transcatheter AVR, and LV ejection fraction <50%). Society of Thoracic Surgeons score was calculated. Standard echocardiography data were obtained. LV-GLS was measured on 2-, 3-, and 4-chamber views using velocity vector imaging. Severe PAS was defined as aortic valve area <0.8 cm², mean aortic valve gradient ≥40 mmHg, and dimensionless index <0.25. A composite outcome of death and congestive heart failure admission was recorded. At baseline, mean Society of Thoracic Surgeons score, LV ejection fraction, mean aortic valve gradients, and right ventricular systolic pressure were 7±6, 58±6%, 54±10 mmHg and 40±14 mmHg, whereas 50% had >2+ aortic regurgitation. Median LV-GLS was -14.2% (-11.4, -17.1%). At 4.2±3 years, 41 (22%) patients met the composite end point (2.5% deaths and 1% strokes at 30 days postoperatively). On multivariable Cox survival analysis, LV-GLS was independently associated with longer-term composite events (hazard ratio, 1.21; 95% confidence interval, 1.10–1.33), *P*<0.01. The C statistic for the clinical model (Society of Thoracic Surgeons score, degree of aortic regurgitation, and right ventricular systolic pressure) was 0.64 (95% confidence interval 0.54–0.79), *P*<0.001. Addition of LV-GLS to the clinical model increased the C statistic significantly to 0.71 (95% confidence interval 0.58–0.81), *P*<0.001.

Conclusions—In asymptomatic/minimally symptomatic patients with severe bioprosthetic PAS undergoing redo AVR, baseline LV-GLS provides incremental prognostic use over established predictors and could potentially aid in surgical timing and risk stratification. (*Circ Cardiovasc Imaging*. 2017;10:e005942. DOI: 10.1161/CIRCIMAGING.116.005942.)

Key Words: aortic valve ■ bioprostheses ■ heart failure ■ reoperation ■ survival analysis

Aortic valve replacement (AVR) is the most commonly performed valvular heart surgery.¹ With growing use of bioprosthetic valves in the current era² and along with improvements in survival of patients undergoing AVR, reoperation to relieve severe prosthetic aortic stenosis (PAS) is increasing. However, there are limited data on long-term outcomes and risk profiles of such patients.^{3–5} In a previous study, we demonstrated excellent long-term outcomes in patients undergoing redo AVR for PAS.⁶ In our report, as well as several others, the presence of symptomatic disease (New York Heart Association [NYHA] functional classes III and IV) before redo surgery was associated with worse outcomes.^{3–9} Therefore, it is essential to further risk stratify patients who

are asymptomatic or minimally symptomatic to better identify the optimal timing of surgery in these patients. This is particularly important because elective redo surgery has a significantly better outcome compared with urgent/emergent surgeries.^{4,5,7,10} Furthermore, with recent advances in percutaneous transcatheter valve-in-valve techniques,¹¹ high-risk patients with prohibitive surgical risk can be alternatively considered for percutaneous procedures.

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The use of left ventricular (LV) global longitudinal strain (GLS) is increasing with many prognostic and clinical

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decision-making implications.¹² In native severe aortic stenosis (AS), LV-GLS is a more sensitive marker of LV systolic function and can decrease in the absence of decline in LV ejection fraction (EF).^{13–15} In these patients, LV-GLS is an independent predictor of longer-term outcomes and can also add incremental prognostic value when used synergistically with other standard risk factors.^{15–18} No large-scale data currently exist in patients with PAS vis-à-vis LV-GLS. Therefore, in asymptomatic or minimally symptomatic patients with severe bioprosthetic AS undergoing redo AVR, we sought to determine whether LV-GLS provides incremental prognostic use, which can help in further risk stratification of these patients.

Methods

Study Population

This is a retrospective observational cohort of 191 consecutive patients with severe bioprosthetic AS who underwent redo AVR at our tertiary care center between 2000 and 2012. Severe PAS was defined as aortic valve (AV) area <0.8 cm², mean AV gradient ≥ 40 mmHg, or dimensionless index <0.25 , according to the guidelines.¹⁹ Patients with mechanical PAS, severe mitral or tricuspid valve disease, and patients who underwent transcatheter AVR were excluded. Patients with LVEF $<50\%$, pacemaker-dependent rhythm, bundle branch block, or atrial fibrillation on resting ECG and patients with NYHA functional classes III and IV symptoms were also excluded.

Clinical Data

After approval by the institutional review board, the clinical data were manually extracted by analysis of electronic medical records. Demographics, clinical data, previous histories, type of AV prosthesis, and indication for the previous AVR were recorded. Severity of symptoms was evaluated by recording NYHA functional class category at the time of index echocardiography in each patient.²⁰ Presence of syncope and angina was also recorded. Cause of the current redo AVR was recorded. The decision for redo surgery was made after thorough evaluation of each patient by the cardiologist and cardiothoracic surgeon at the time of initial evaluation. We also recorded whether the redo surgery was elective or urgent (defined as done as part of a hospitalization because of endocarditis or an inpatient transfer from an outside institution). For each patient, Society of Thoracic Surgeons (STS) score was calculated to predict risk of postoperative mortality. Patients were divided into 2 groups based on their STS score: low (score of <4) and intermediate/high (STS score of ≥ 4), based on recent guidelines.²¹ Details of redo surgery, including the type and size of the new valve and other concurrent surgeries, such as coronary artery bypass grafting (CABG) or aortic surgeries, were recorded.

Echocardiographic Data

Preoperative Echocardiography

All patients underwent a comprehensive echocardiogram using commercially available instruments (Philips Medical Systems, NA, Bothell, WA; General Electric Medical Systems, Milwaukee, WI; and Siemens Medical Solutions USA Inc, Malvern, PA). Measurements and recordings were done according to the guidelines.^{22,23} LV dimensions (end systolic and end diastolic), LV mass, and left atrial dimensions were obtained from 2-dimensional images and indexed to body surface area. LVEF was measured using Simpson biplane method. A semiquantitative 5-point scale (none, mild, moderate, moderate–severe, and severe) was used to quantify valvular regurgitation.²⁴ Right ventricular systolic pressure (RVSP) was measured at rest, according to guidelines, using the following formula: $4 \times (\text{tricuspid regurgitant velocity [m/s]})^2 + \text{right atrial pressure (mmHg)}$.²⁵ Right atrium pressure was estimated from inferior vena cava diameter and respiratory changes as follows: 3 mmHg (inferior vena cava ≤ 2.1 cm, collapse with sniff $>50\%$), 8 mmHg

(inferior vena cava >2.1 cm, collapse $>50\%$), and 15 mmHg (inferior vena cava >2.1 cm, collapse with sniff $<50\%$).²⁵

Severity of PAS was assessed according to the guidelines.¹⁹ LV outflow tract diameter was measured in parasternal long-axis views. Velocities across the LV outflow tract and AV were measured by pulsed-wave and continuous-wave Doppler, respectively. AV was examined from multiple windows to obtain the peak AV velocity and mean AV gradient. AV area was calculated by continuity equation. Severe PAS was defined as AV area <0.8 cm², mean AV gradient ≥ 40 mmHg, or dimensionless index <0.25 .

Left Ventricular Global Longitudinal Strain

LV-GLS measurements were obtained from baseline resting transthoracic echocardiograms using gray-scale images recorded in apical 2-, 3-, and 4-chamber views. LV-GLS was analyzed offline using velocity vector imaging (Syngo VVI, Siemens Medical Solutions, Mountain View, CA), as previously described.¹⁸ All raw data were stored in Digital Imaging and Communications in Medicine format without compression. The frame rate was at least 30 frames per s. After manual definition of the LV endocardial border, the endocardium was automatically tracked throughout the cardiac cycle. Global LV strain was obtained by averaging all segmental strain values from all 3 apical views. Peak global strain was defined as the peak negative value on the strain curve during the entire cardiac cycle. All measurements were made offline by an investigator blinded to all clinical and demographic information (P.N.). Measurements were averaged over 3 cardiac cycles. As the reported LV-GLS values are negative, a lower absolute number represented a worse value than higher (Figure 1). In 10 randomly selected patients, LV-GLS values were remeasured twice by an investigator (M.Y.D.) at least 1 month apart.

Postoperative Echocardiography

We evaluated postoperative follow-up echocardiograms for LVEF and AV gradients. In addition, we recorded different types and sizes of implanted AV prostheses, including bioprostheses, mechanical prostheses, and homografts. Subsequently, to determine the presence of patient–prosthesis mismatch, we recorded the effective orifice areas of the PAV, in each patient and indexed it to body surface area.¹⁹ Normal indexed effective orifice areas values are >0.85 cm²/m². Patient–prosthesis mismatch was categorized as severe if indexed effective orifice areas was <0.65 cm²/m² and moderate if indexed effective orifice areas was between 0.65 and 0.85 cm²/m².¹⁹

Outcomes Assessment

Adverse outcomes, including death, development of congestive heart failure (CHF), and stroke, were recorded with their respective dates for each patient. The duration of follow-up ranged from time of redo AVR to time of last follow-up at our institution. Mortality, including 30-day postoperative death, was confirmed by observation of death certificate or verified with a family member. In this study, there were no documented noncardiac deaths during follow-up. In addition, CHF was defined as meeting the criteria for stage C or D of American College of Cardiology/American Heart Association classification of CHF.²⁶ A composite end point of death and admission for CHF was recorded. CHF admissions were identified as follows: (1) patients needing an admission within our health system were identified through our electronic medical records and (2) patients needing an admission outside our health system were identified through annual questionnaires. Postoperative stroke, defined as a neurological impairment lasting >24 hours because of cerebral ischemia or hemorrhage confirmed by radiographic studies, was also recorded. Transient ischemic attack was similarly defined as neurological impairment lasting <24 hours. The confirmatory testing for neurological events included a clinically indicated magnetic resonance and tomographic scans, which were ordered based on clinical assessment of the patient, in conjunction with a neurology consultation.

Statistical Analysis

Continuous variables are expressed as mean \pm SD or median and interquartile range (IQR) for skewed distributions. Categorical data

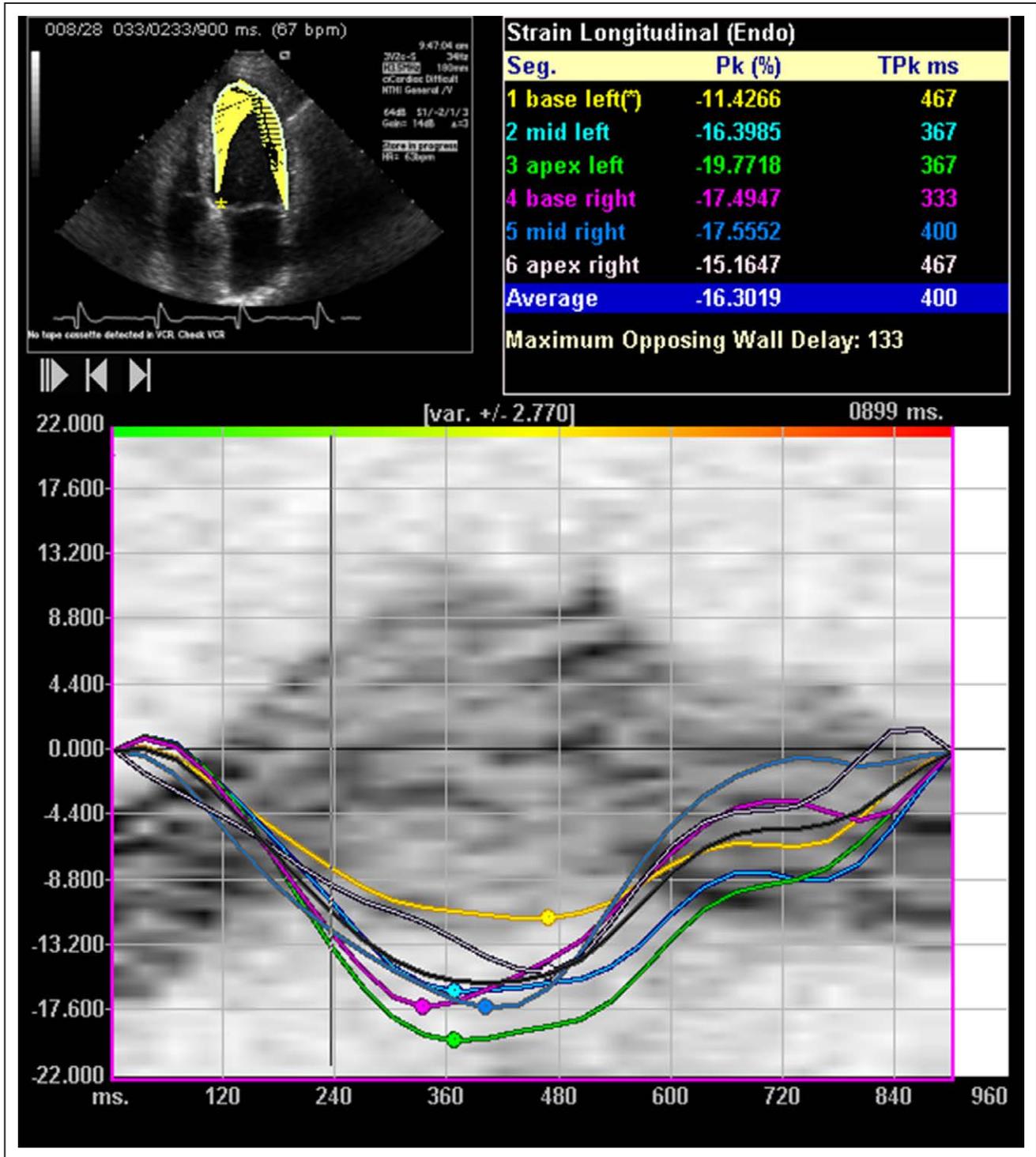


Figure 1. Representative example of left ventricular global longitudinal strain from the study sample.

are expressed as percentage. Spearman correlation coefficient was used to assess correlation between continuous variables. Variability for LV-GLS measurements was assessed using intraclass correlation coefficients. To assess outcomes, Cox proportional hazards analysis was performed. We created a parsimonious model in which prespecified relevant variables, associated with adverse outcomes in PAS patients, were included. As we have demonstrated in a previous study, even though STS score has only been validated to predict 30-day postoperative mortality, we used it in the longer-term outcome analysis because it is a composite of many factors that are known to be associated with adverse postoperative events in the longer term.²⁷

Hazard ratios with 95% confidence intervals (CIs) were calculated. To confirm that proportional hazards assumption was not violated, graphical inspection of Schoenfeld residuals plotted against time was performed. In addition, using Kaplan–Meier survival analysis, cumulative proportion of events as a function over time were generated, and statistical significance of the event was compared using log-rank statistic. We also assessed the reclassification of risk of longer-term outcomes using category free integrated discrimination index (for continuous variables) and net reclassification improvement (for categorical variables).²⁸ In addition, discriminative ability of various survival models was compared using the Harrell C statistic for time

to event outcomes. Statistical analysis was performed using SPSS version 11.5 (SPSS Inc, Chicago, IL) and R 3.0.3 (R foundation for Statistical Computing, Vienna, Austria). A *P* value of <0.05 was considered significant.

Results

The baseline and clinical data in the study sample are shown in Table 1. The preoperative risk was expectedly high with an expected distribution of cardiovascular risk factors. The vast majority of the patients (77%) had dyspnea and were deemed to be in NYHA class II. Patients that deemed themselves to be in NYHA class I had other signs/symptoms (severe aortic regurgitation with a dilated LV or endocarditis-related signs/symptoms, such as fever, weight loss, night sweats, large mobile echo-density on echocardiography, etc) at presentation, which necessitated redo cardiac surgery. Although the majority (90%) had 1 previous open heart surgery, a sizable proportion of patients (10%) had multiple previous open heart surgeries. The baseline risk for perioperative mortality was expectedly high with a mean STS score of $7\pm 6\%$ (median, 6.9; IQR, 2.9–10.5). Also, the Charlson comorbidity index was high at 2.98 ± 2 . There was a significant correlation between STS score and Charlson index ($r=0.48$; $P<0.001$). Baseline echocardiographic data in the study sample are shown in Table 2. By study design, all patients had a preserved LVEF ($\geq 50\%$), whereas 50% had $>2+$ AR. The median LV-GLS was -14.2% (IQR, -17.1% to -11.4%). There was a significant correlation between baseline LVEF and LV-GLS ($r=-0.42$, $P<0.001$). The intraclass correlation coefficients for intraobserver (M.Y.D.) and interobserver (P.N. and M.Y.D.) agreement for LV-GLS measurements was as follows: 0.91 (95% CI, 0.83–0.97) and 0.88 (95% CI, 0.80–0.94), both $P<0.001$.

The distribution of subsequent redo cardiac surgeries was as follows: (1) isolated AVR (n=79, 41%), (2) AVR+CABG (n=54, 28%), and (3) AVR+aortic surgery±CABG (n=58, 30%). Of the patients who underwent concomitant CABG, 70% needed multi-vessel revascularization. Distribution of different valve types that were implanted was as follows: bioprosthesis (n=143, 75%), mechanical prosthesis (n=21, 11%), and homograft (n=27, 14%).

The mean time between previous and current AVR was 9 ± 5 years (median, 8.5 years; IQR, 6.2–11.7). Results of postoperative echocardiogram are shown in Table 2. The peak and mean gradients across the newly implanted prosthetic valves were 24 ± 12 and 13 ± 7 mmHg, respectively. There was a significant correlation between postoperative LVEF and baseline LV-GLS ($r=-0.21$; $P=0.007$).

Outcomes Assessment

Transient atrial fibrillation (within 30 days postoperatively) was seen in 48 (25%) patients (new transient atrial fibrillation noticed in 18 patients), whereas permanent atrial fibrillation (throughout the length of follow-up) was seen in 15 (8%) patients. At 4.2 ± 3 years (median, 3.4 years; IQR, 1.8–5.9), 41 (22%) patients met the composite end point (26 deaths and 15 CHF admissions). No patient had an overt noncardiac cause to account for their deaths during follow-up. At 30 days postoperatively, there were 5 (2.5%) deaths and 2 (1%) strokes.

Table 1. Baseline Characteristics of the Study Sample (n=191)

	Total Sample (n=191)
Age, y	63±16
Male sex	110 (58%)
Body surface area, m ²	2±0.3
Angina	63 (33%)
Syncope	13 (7%)
New York Heart Association class	
I	43 (23%)
II	148(77%)
Hypertension	123 (64%)
Hyperlipidemia	95 (50%)
Diabetes mellitus	45 (27%)
Previous stroke	15 (8%)
Current smoker	16 (8%)
Obstructive coronary artery disease	77 (40%)
Atrial fibrillation	37 (19%)
Previous open heart surgeries	
1	171 (90%)
2	18 (9%)
≥3	1 (1%)
Indications for initial aortic valve replacement	
Calcific	147 (77%)
Bicuspid	27 (14%)
Endocarditis	12 (6%)
Rheumatic	5(3%)
Sizes of previous aortic valve bioprostheses	
19	29 (15%)
21	61 (32%)
23	50 (26%)
25	36 (19%)
27	15 (8%)
Pacemaker/internal defibrillator	23 (12%)
Society of Thoracic Surgeons score	7±6 (median, 6.9; interquartile range, 2.9–10.5)
Charlson Comorbidity Index	2.98±1.8
β-blockers	103 (54%)
Angiotensin-converting enzyme inhibitors	134(28) (48%)
Aspirin	109 (57%)
Statins	119(43%)
Diuretics	79 (41%)
Calcium supplements	23 (12%)
Vitamin D supplements	27 (14%)
Hemoglobin, mg/dL	13±2

(Continued)

Table 1. Continued

	Total Sample (n=191)
Glomerular filtration rate, mL min ⁻¹ 1.73 m ⁻²	75±25
Low-density lipoprotein, mg/dL	101±32
High-density lipoprotein, mg/dL	49±17
Indication for current surgery	
Prosthesis deterioration	181 (95%)
Infective endocarditis	10 (5%)
Timing of surgery	
Elective	134 (70%)
Urgent	57 (30%)

On univariable Cox Proportional Survival Analysis (Table 3), the following predictors were associated with worse longer-term composite outcomes: STS score, Charlson comorbidity index, increasing age, NYHA class, low glomerular filtration rate, worse degree of AR, higher RVSP, and worse LV-GLS. Subsequently, selected relevant predictors were entered into a multivariable model, the results of which are shown in Table 4. Higher STS score (HR, 1.12; 95% CI, 1.07–1.17), higher grades of AR (HR, 2.08; 95% CI, 1.13–3.84), higher RVSP (HR, 1.71; 95% CI, 1.40–2.10), and resting LV-GLS (HR, 1.21; 95% CI, 1.10–1.33) before the current redo AVR were associated with worse longer-term outcomes (all $P<0.001$). All continuous variables met linearity assumptions and were not transformed for entry into multivariable analysis.

The C statistic for the clinically relevant model (STS score, degree of AR, and RVSP) was 0.64 (95% CI, 0.54–0.79), $P<0.001$. Addition of LV-GLS to the clinical model increased the C statistic significantly to 0.71 (0.58–0.81), $P<0.001$. Similarly, addition of LV-GLS to the clinical model increased the categorical net reclassification improvement from 0.25 (0.18–0.41) to 0.36 (0.21–0.54), $P<0.001$. Also, addition of LV-GLS to the STS score (both continuous variables) increased the integrated discrimination index from 0.07 (0.03–0.12) to 0.14 (0.06–0.19), $P<0.001$.

The proportion of adverse longer-term outcomes in the sample, separated on the basis of STS score cutoff of 4, was significantly different as follows: 4 of 52 (8%) in the group with STS score of <4 versus 37 of 139 (27%) in the group with STS score of ≥ 4 (log-rank statistic $P<0.001$). Unadjusted Kaplan–Meier survival curves, demonstrating the longer-term outcomes in the study sample, separated on basis of STS score, are shown in Figure 2. The proportion of adverse longer-term outcomes in the sample, separated on the basis of LV-GLS better or worse than median (–14.2%), were significantly different as follows: 11 of 96 (12%) in patients with LV-GLS better than median versus 30 of 95 (32%) in patients with LV-GLS worse than median (log-rank statistic $P<0.001$). Unadjusted Kaplan–Meier survival curves, demonstrating the longer-term outcomes in the study sample, separated on basis of LV-GLS, are shown in Figure 3.

Subsequently, we created the following 4 subgroups based on STS score cutoff of 4 and LV-GLS better or worse

Table 2. Baseline and Follow-Up Echocardiographic Characteristics of the Study Sample (n=191)

	Total Sample (n=191)
Preoperative echocardiography	
LV ejection fraction (%)	58±4
Indexed LVEDD, cm/m ²	2.3±0.5
Indexed LVESD, cm/m ²	1.6±0.4
Indexed LA dimension, cm/m ²	2.3±0.5
Indexed LV mass, g/m ²	138±52
Diastolic dysfunction	
Abnormal relaxation	162 (84%)
Pseudonormal	28 (14%)
Restrictive filling	1 (0.05%)
AV gradient	
Peak, mm Hg	90±21
Mean, mm Hg	54±17
Calculated AV area (continuity equation)	0.69±0.2
Aortic dimension at midascending segment, cm	3.43±0.7
At least moderate aortic regurgitation	95 (50%)
Mitral regurgitation	
None	29 (15%)
Mild	86 (45%)
Moderate	76 (40%)
Tricuspid regurgitation	
None	33 (17%)
Mild	110 (58%)
Moderate	48 (25%)
RVSP, mm Hg	40±15
LV-GLS (%)	–14.2±4
Postoperative echocardiography	
LV ejection fraction (%)	52±11
AV gradient	
Peak, mm Hg	24±12
Mean, mm Hg	13±7
Indexed EOA of prosthetic valve, cm ² /m ²	0.89±0.14
Patient–prosthesis mismatch	
None	137 (72%)
Moderate	50 (26%)
Severe	4 (2%)

AV indicates aortic valve; EDD, end-diastolic dimension; EOA, effective orifice areas; ESD, end-systolic dimension; LA, left atrium; LV, left ventricle; LV-GLS, left ventricular global longitudinal strain; and RVSP, right ventricular systolic pressure.

than median. The proportion of adverse longer-term outcomes in the 4 subgroups were significantly different (log-rank statistic $P<0.001$). (1) STS score of <4, LV-GLS better than median: 1 of 31 (3%), (2) STS score of ≥ 4 and LV-GLS

Table 3. Univariable Cox Proportional Hazard Survival Analysis for the Composite End Point in the Study Population

Variable	Hazard Ratio (95% CI)	P Value
Age (for 10-y increase)	1.49 (1.22–1.82)	<0.001
Male sex	1.522 (0.77–3.00)	0.21
New York Heart Association class (I vs II)	1.14 (1.01–2.01)	0.04
Hypertension	1.12 (0.57–2.22)	0.73
Hyperlipidemia	1.06 (0.56–2.01)	0.84
Diabetes mellitus	1.32 (0.85–2.34)	0.29
Obstructive coronary artery disease	1.70 (0.91–3.16)	0.10
Stroke	1.40 (0.80–2.50)	0.58
Smoking	1.10 (0.41–2.73)	0.82
No. of previous cardiac surgery	1.24 (0.69–3.14)	0.56
STS score (for every unit increase)	1.12 (1.07–1.16)	<0.001
Charlson comorbidity index	1.40 (1.17–1.68)	<0.001
Aspirin	0.64 (0.34–1.22)	0.17
β -blockers	0.75 (0.39–1.42)	0.37
Angiotensin-converting enzyme inhibitors	0.93 (0.50–1.73)	0.81
Statins	0.73 (0.41–1.59)	0.58
Diuretics	1.29 (0.73–2.41)	0.43
Glomerular filtration rate (for every 10 U decrease)	1.22 (1.06–1.40)	0.005
Indexed left atrial dimensions	1.02 (0.81–1.52)	0.52
Indexed left ventricular end-systolic dimension	1.29 (0.74–2.32)	0.44
Indexed left ventricular mass (for 10 g/m ² increase)	1.02 (0.96–1.08)	0.49
Left ventricular ejection fraction (for every 10% reduction)	1.21 (1.05–1.64)	0.01
Mean aortic valve gradient (10 mm Hg worsening)	1.08 (0.92–1.27)	0.29
≥ 2 +aortic regurgitation	2.34 (1.21–4.53)	0.01
Right ventricular systolic pressure (for every 10 mm Hg increase)	1.49 (1.29–1.72)	<0.001
Left ventricular global longitudinal strain	1.15 (1.06–1.24)	0.002
Indication for current surgery: prosthesis deterioration vs others	1.16 (0.43–3.02)	0.69
Timing of surgery (elective vs urgent)	1.51 (0.90–2.41)	0.11
Type of cardiac surgery performed (isolated AVR vs combination procedure)	1.03 (0.77–1.29)	0.31
Time between previous and redo AVR	1.01 (0.97–1.02)	0.83
Type of valve prosthesis implanted (bioprosthesis vs other)	0.83 (0.54–1.17)	0.31
Patient–prosthesis mismatch (none vs moderate/severe)	1.19 (0.69–1.97)	0.57

AVR indicates aortic valve replacement; and STS, Society Of Thoracic Surgeons.

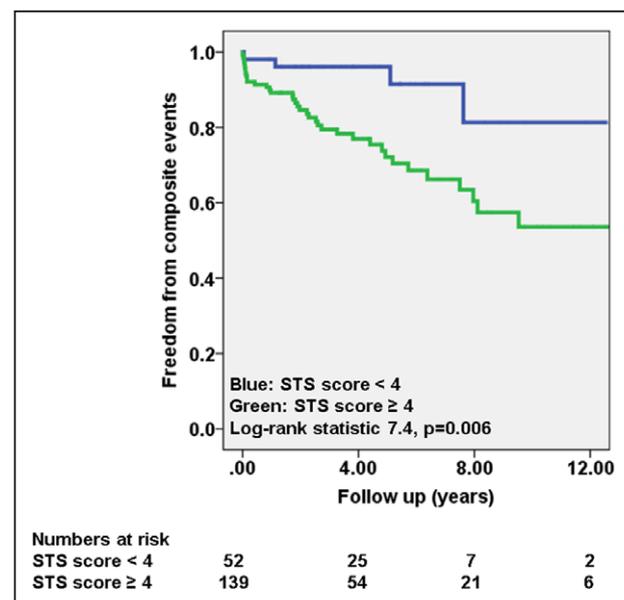
Table 4. Multivariable Cox Proportional Hazard Analysis for Longer-Term Composite Outcomes in the Study Population

Variable	Hazard Ratio (95% CI)	P Value
STS score (for every unit increase)	1.12 (1.07–1.17)	<0.001
≥ 2 +aortic regurgitation at presentation	2.08 (1.13–3.84)	0.001
Right ventricular systolic pressure (for every 10 mm Hg increase)	1.71 (1.40–2.10)	<0.001
Baseline LV-GLS (for every unit increase)	1.21 (1.10–1.33)	<0.001
χ^2 for the model=67, $P<0.0001$		

Because Society of Thoracic Surgeons (STS) score was included in the multivariable model, individual predictors that comprise the STS score were not included. Because of significant collinearity between STS score and Charlson comorbidity index, only STS score was included in multivariable analysis. The results were similar if Charlson index was substituted for STS score. CI indicates confidence interval; and LV-GLS, left ventricular global longitudinal strain.

better than median: 10 of 65 (15%), (3) STS score of <4 and LV-GLS worse than median: 3 of 21 (14%), and (4) STS score of ≥ 4 and LV-GLS worse than median: 27 of 74 (37%). Unadjusted Kaplan–Meier survival curves, demonstrating the longer-term outcomes in the study sample, separated on basis of these 4 subgroups, are shown in Figure 4. The association was similarly significant, even after adjustment of variables listed in Table 4.

When multivariable Cox proportional hazards survival analysis was performed with exclusion of patients with concomitant obstructive coronary artery disease (total study sample 114, number of composite events=30), worsening STS score (HR, 1.09; 95% CI, 1.04–1.13; $P=0.001$) and LV-GLS (HR, 1.13; 95% CI, 1.05–1.39; $P=0.005$) were significantly associated with longer-term adverse events. Similarly, when multivariable Cox proportional hazards survival analysis was performed with only mortality as an end point ($n=25$), worsening STS score (HR, 1.07; 95% CI, 1.02–1.13; $P=0.01$) and

**Figure 2.** Kaplan–Meier survival curves of the study sample, separated on the basis of Society of Thoracic Surgeons (STS) score cutoff of 4.

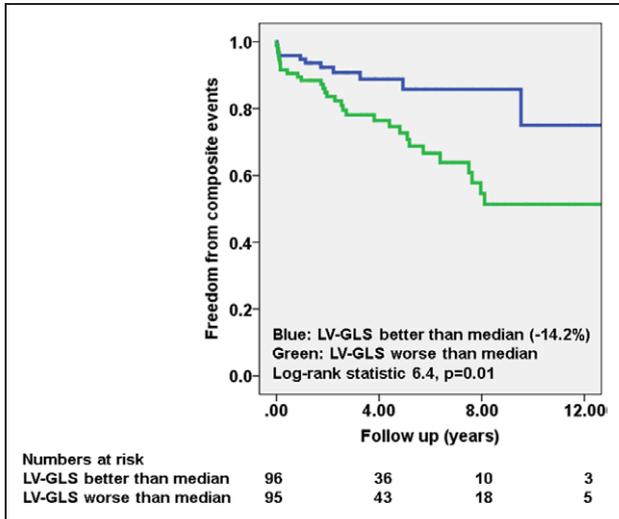


Figure 3. Kaplan–Meier survival curves of the study sample, separated on the basis of left ventricular global longitudinal strain (LV-GLS) better or worse than median (–14.2%).

LV-GLS (HR, 1.12; 95% CI, 1.02–1.36; $P=0.01$) were still significantly associated with longer-term mortality.

Discussion

This study demonstrates that in asymptomatic or minimally symptomatic patients with severe bioprosthetic AS and preserved LVEF undergoing redo surgical AVR, LV-GLS is independently associated with composite outcome of longer-term death or admission for CHF. Furthermore, LV-GLS provides incremental prognostic use when added to other established risk factors and significantly reclassifies risk of longer-term adverse events. Patients with LV-GLS worse than median had significantly higher rate of longer-term adverse events compared with those whose LV-GLS was better than median. Furthermore, the longer-term outcomes of the subgroup with STS score of ≥ 4 and LV-GLS worse than median were significantly higher than the other subgroups, including those with an STS

score of ≥ 4 but LV-GLS better than median. This suggests that using LV-GLS could potentially help time an earlier invasive intervention in such patients. Similar to previous reports in native severe AS, this study demonstrates the incremental prognostic value of LV-GLS when added to other standard risk factors in predicting outcomes of patients with severe PAS.^{16–18,29} However, to the best of our knowledge, this is one of the largest studies to evaluate the prognostic use of LV-GLS in predicting the outcomes of this challenging and increasingly encountered patient population with severe PAS.

Our patients had excellent short- and long-term survival rates after their redo AVR. Although the perioperative mortality was estimated at 7% by STS score, we observed an actual 30-day mortality of 2.5% (0.6% for isolated AVR) which was better than the rates of 4.5% to 10.6% as reported in the literature.^{3–5} Complexity of surgery was also higher in our patients, and only 41% of our patients underwent isolated redo AVR; however, it was not associated with adverse events. Patient–prosthesis mismatch was also not associated with adverse events. Presence of coronary artery disease or undergoing concomitant CABG did not adversely affect the outcomes. Furthermore, even in patients without documented obstructive coronary artery disease, LV-GLS was associated with increased longer-term adverse events.

Increasing STS score, higher RVSP, and concomitant $\geq 2+$ AR on presentation were the other independent predictors of adverse long-term outcomes in our study. In a previous larger study (which also included symptomatic patients), these factors had emerged as independent predictors of outcomes,⁶ and they have remained significant in asymptomatic patients as well. Concomitant $\geq 2+$ AR can point to a more severe bioprosthesis deterioration, and recent data suggest that patients with mixed AV stenosis and regurgitation are at increased risk of adverse events.³⁰ Higher RVSP is also reflective of advanced stage of disease and has been associated with worse outcomes in a wide range of valvular heart diseases.³¹

Median LV-GLS was –14.2% in our study sample, which is comparable to LV-GLS in patients with severe native AS,^{14,15,18}

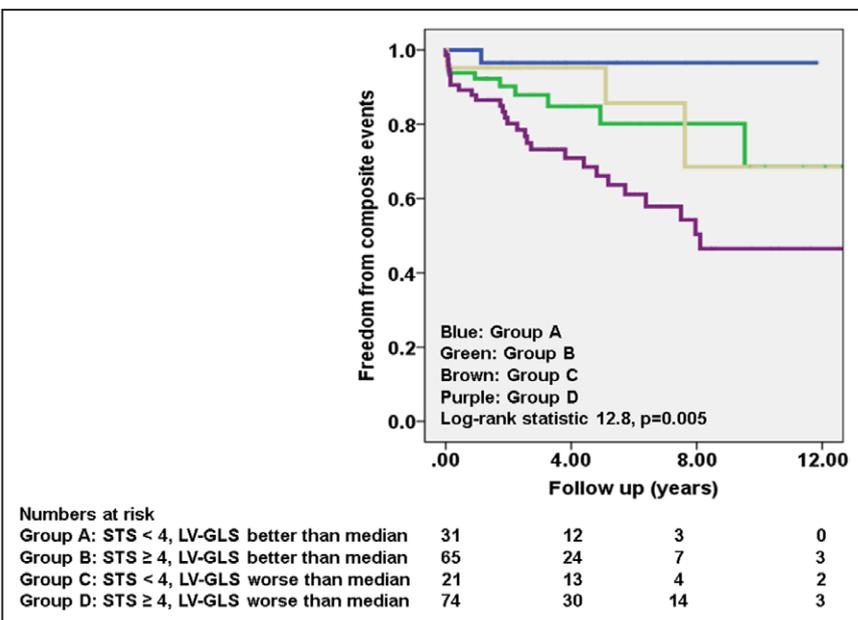


Figure 4. Kaplan–Meier survival curves of the study sample, separated on the basis of 4 subgroups: Group A: Society of Thoracic Surgeons (STS) score of <4, left ventricular global longitudinal strain (LV-GLS) better than median, group B: STS score of ≥ 4 and LV-GLS better than median, group C: STS score of <4 and LV-GLS worse than median, and group D: STS score of ≥ 4 and LV-GLS worse than median.

but lower than normal population.^{32,33} Of note, the observed reduction in LV-GLS in our patients had occurred in spite of preserved resting LVEF and having no or minimal symptoms. From a pathophysiologic perspective, with increasing severity of PAS, there is increased LV systolic pressure overload which causes LV hypertrophy, subendocardial ischemia, and myocardial fibrosis.³⁴ These ultimately lead to systolic dysfunction and a drop in LVEF, which has been demonstrated to be associated with adverse outcomes. LV-GLS is mainly affected by increased stress in the subendocardial layer, whereas LVEF does not drop until the process is more transmural.³⁵ Thus, LV-GLS is a more sensitive marker and reflects the myocardial dysfunction at an earlier stage before the onset of overt LV failure. LV-GLS correlates closely, and better than LVEF, with the extent of myocardial fibrosis.³⁶ Myocardial fibrosis does not reverse after AV surgery,³⁶ and patients with higher degree of fibrosis have worse postoperative symptoms³⁶ and all-cause mortality.³⁷ LV-GLS can therefore be of special importance in risk stratification of patients who have normal LVEF and are not symptomatic yet.

Clinical Implications

On the basis of the current guidelines, the indications for redo AVR for PAS are similar to those of native AS.³¹ Although the management is more straightforward in patients who develop symptomatic disease or LV dysfunction, the surgical decision-making remains challenging in patients with severe disease but without symptoms or LV impairment. In this study, we specifically targeted this challenging subpopulation and were able to identify higher-risk patients who can potentially benefit from earlier surgery, especially at an experienced center. Assessment of LV-GLS is a noninvasive and fast method that can detect myocardial dysfunction at an early stage and can significantly aid in risk stratification of asymptomatic patients. Majority of our patients were in intermediate- or high-risk surgical groups based on their STS scores. Although we observed excellent surgical outcomes at our experienced center, percutaneous valve-in-valve techniques are also rapidly evolving and can provide alternate options in patients who are deemed to be at a prohibitive risk of surgery.

Limitations

This is an observational study conducted at a tertiary care center and likely not free from referral bias. This was the first study to evaluate the role of LV-GLS in patients with severe bioprosthetic AS. Although the sample size is relatively small, it is the largest experience in patients with severe bioprosthetic AS who underwent redo cardiac surgery. Although our results are not easily comparable with other studies in the literature, they were concordant with most studies in patients with native AS.^{13–18} Measurement of LV-GLS requires additional software but is widely available. Velocity vector imaging is vendor-independent strain software that is relatively easy to use, but its clinical use remains unproven. Also, cutoffs of normal versus abnormal LV-GLS values may vary with different analysis softwares, and hence, the results may not be generalizable across imaging platforms. Both LV-GLS and LVEF are affected by loading conditions of the LV, but LV-GLS is less affected by geometry of LV and has good reproducibility

and interobserver variability.^{32,35,38} By design, patients with low-flow, low-gradient PAS were not included in our study; however, strain parameters are strong predictors of outcomes in these patients in native AS.^{39,40}

Conclusions

In asymptomatic or minimally symptomatic patients with severe bioprosthetic AS and preserved LVEF undergoing redo surgical AVR, LV-GLS is an independent predictor of longer-term adverse events, providing incremental prognostic use and significantly reclassifying risk of longer-term adverse events. Patients with LV-GLS worse than the median had significantly higher rate of adverse outcomes compared with those whose LV-GLS was better than median. Furthermore, the longer-term adverse events in the subgroup with STS score of ≥ 4 and LV-GLS worse than median were significantly worse than the other subgroups, including those with an STS score of ≥ 4 but LV-GLS better than median. This suggests that using LV-GLS could potentially help time an earlier invasive intervention in such patients. Future prospective data are required to ascertain the findings of this study.

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Disclosures

Dr Gillinov is on speakers' bureau for Atricure, Edwards, Medtronic, and St. Jude's Medical. He also reports equity stake in Pleurafflow. Dr Johnston is a consultant for Edwards, St. Jude's Medical, KEF, and Integrated Visual Health Record. Dr Desai is a consultant for Myokardia, Inc. The other authors report no disclosures.

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CLINICAL PERSPECTIVE

In asymptomatic/minimally symptomatic patients with severe bioprosthetic aortic stenosis and preserved left ventricular ejection fraction undergoing redo surgical aortic valve replacement, left ventricular global longitudinal strain is an independent predictor of longer-term adverse events, providing incremental prognostic use and significantly reclassifying risk for adverse events. The longer-term adverse events in the subgroup with Society of Thoracic Surgeons score of ≥ 4 and left ventricular global longitudinal strain worse than median were significantly worse than the other subgroups, including those with a Society of Thoracic Surgeons score of ≥ 4 but left ventricular global longitudinal strain better than median. This suggests that using left ventricular global longitudinal strain could potentially help time an earlier invasive intervention in such patients.

Incremental Prognostic Use of Left Ventricular Global Longitudinal Strain in Asymptomatic/Minimally Symptomatic Patients With Severe Bioprosthetic Aortic Stenosis Undergoing Redo Aortic Valve Replacement

Peyman Naji, Shailee Shah, Lars G. Svensson, A. Marc Gillinov, Douglas R. Johnston, L. Leonardo Rodriguez, Richard A. Grimm, Brian P. Griffin and Milind Y. Desai

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